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(54) Title: **GABAPENTIN TABLET AND METHOD OF MAKING WITH IMPROVED PHYSICAL AND CHEMICAL CHARACTERISTICS**

(57) Abstract: A pharmaceutical formulation form with improved physical and chemical characteristics, comprising gabapentin in tablet form for oral administration. The tablet form can be prepared by spray-coating gabapentin with a binder solution and compressing the spray-coated gabapentin into non-friable, stable tablets. This method is particularly useful for tablet formulations that require large doses of active drug.

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GABAPENTIN TABLET AND METHOD OF MAKING WITH IMPROVED PHYSICAL AND CHEMICAL CHARACTERISTICS

BACKGROUND OF THE INVENTION

5 1. *Field Of The Invention*

 This invention is generally directed to pharmaceutical formulations with improved physical and chemical characteristics, comprising gabapentin in tablet form for oral administration. The tablet form can be prepared by spray-coating gabapentin with a binder solution and compressing the spray-coated gabapentin
10 into non-friable, stable tablets. This invention is also generally directed to a method of producing pharmaceutical formulations in tablet form which contain large doses of active drug by spray-coating the active drug with a binder solution and compressing the spray-coated active drug into tablets.

15 2. *Description of the Related Art*

 Prior art methods for improving the compression characteristics of pharmaceutical formulations involve introducing additional excipients, such as microcrystalline cellulose, as compression aids to prevent fracturing of granules and tablets. However, the inclusion of additional excipients can be expensive and time consuming, can effect the stability of the active drug agent, and can increase
20 the size of the tablet.

 Other methods for improving the compression characteristics of pharmaceutical formulations include dissolving the active drug in a binder solution to form a drug solution, spray drying the drug solution to form a powder and then compressing the powder into a tablet. This method, however, is inefficient
25 because it requires a large amount of binder solution. Moreover, dissolving the active drug in a solution can cause stability problems, polymorph conversion, and changes in the crystalline structure of the drug.

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U.S. Patent No. 4,874,614 issued to Becker, discloses a method of preventing the fracture of coated drug granules during the compression process by incorporating into a matrix, along with the granules, microcrystalline cellulose in the amount from 10% to 50% by weight of the total matrix.

5 U.S. Patent No. 5,725,884, issued to Sherwood et al., discloses the use of a microcrystalline cellulose based excipient comprising microcrystalline cellulose and silicon dioxide to improve the compressibility of the excipient microcrystalline cellulose, not the active drug substance.

10 U.S. Patent No. 5,534,551, U.S. Patent No. 4,533,674, U.S. Patent No. 4,605,666 and U.S. Patent No. 4,710,519 all disclose a method of producing a compressible tablet by dissolving the active agent in a solvent and a binder then spray drying the solution to obtain a spray dried powder that is suitable for direct compression.

15 IE 3089/90 to issued Augart, et. al., discloses a process for stabilizing pharmaceutical compositions containing gabapentin in solid form. The process entails hydrolyzing gabapentin with a semi-concentrated mineral acid and then converting gabapentin into a solid pharmaceutical composition containing hydroxypropyl methylcellulose, polyvinylpyrrolidone, crospovidone, maize starch, cyclodextrin, talcum, co-polymer of dimethylaminomethacrylic acid and/or neutral
20 methacrylic acid ester.

Various patent applications and patents disclosing processes for preparing the gabapentin, and its methods of use are disclosed in PCT 98/28255, U.S. Patent No. 4,024,175, U.S. Patent No. 4,087,544, U.S. Patent No. 5,084,479, U.S. Patent No. 4,960,931, and U.S. Patent No. 4,894,476.

25

BRIEF SUMMARY OF THE INVENTION

It has been discovered that pharmaceutical formulations containing the active drug gabapentin can be produced with large doses of gabapentin but still be

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small enough for a patient to swallow. It has also been discovered that pharmaceutical formulations containing gabapentin in tablet form can be produced having improved characteristics such as hardness, friability and stability. It has further been discovered that the pharmaceutical formulations containing

5 gabapentin can be produced in tablet form by spray-coating gabapentin particles with a binder solution and compressing the spray-coated particles into tablets. This method is also applicable to other pharmaceutical tablet formulations that require large doses of active drug for oral administration.

Thus, one aspect of the present invention is a pharmaceutical tablet

10 comprising more than about 76% by weight of gabapentin. A second aspect of the invention is a pharmaceutical tablet comprising more than about 76% by weight of gabapentin, a friability of less than about 1%, a hardness of about 10 kp to about 20 kp and a lactam level, a major degradation product of gabapentin, of less than about 0.4% by weight of the tablet composition.

15 A first preferred embodiment of the invention is that the pharmaceutical tablet comprises more than about 88% by weight of gabapentin. A second preferred embodiment is that the tablet has a friability of less than about 0.8%. A third preferred embodiment is that the tablet has a hardness of about 14 kp to about 16 kp. A fourth preferred embodiment of the invention is that the tablet has

20 a lactam level of less than 0.2%.

An additional aspect of the invention is a pharmaceutical tablet comprising more than about 76% by weight of gabapentin, said tablet being formed from gabapentin particles spray-coated with a binder solution, mixed with a disintegrant and a lubricant, and then compressed into the tablet.

25 Another aspect of the invention is a method of producing a pharmaceutical tablet comprising:

dissolving binder in a solvent to produce a binder solution;

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spray-coating the binder solution on gabapentin particles to achieve spray-coated gabapentin particles; and

compressing the spray-coated gabapentin particles into a tablet for oral administration to a patient,

5 where the tablet contains more than 76% by weight of gabapentin.

A further aspect of this invention is a method of producing a pharmaceutical tablet comprising:

dissolving binder in a solvent to produce a binder solution;

10 spray-coating the binder solution on active drug particles to achieve spray-coated active drug particles; and

compressing the spray-coated active drug particles into a tablet for oral administration to a patient,

where the tablet contains about 500 mg to about 1200 mg of active drug.

15 With the foregoing and other objects, advantages and features of the invention that will become herein after apparent, the nature of the invention may be more clearly understood by reference to the following detailed description and to the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

20 FIG. 1 shows a plot of tablet hardness versus compression force for tablets produced by traditional dry and wet granulation methods versus tablets made in accordance with Example 1.

FIGS. 2 and 3 show a plot of tablet hardness versus compression force for tablets containing, respectively, 600 mg and 800 mg of gabapentin made in accordance with Example 1.

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DETAILED DESCRIPTION OF THE INVENTION

The development of a pharmaceutical composition is often a laborious task. However, if the active drug has poor compressibility and compaction properties, developing economically efficient manufacturing processes can be painstaking.

5 Additionally, if the active drug is incompatible with excipients commonly used in pharmaceutical formulations, the task of developing the pharmaceutical composition may require extensive experimentation. This task can be further complicated by size limitations of a tablet to be comfortably swallowed by the patient, dissolution rate limitations for bioavailability considerations and durability
10 requirements to successfully survive the film coating process or other handling procedures. These problems were overcome in the preparation of a pharmaceutical composition for this invention.

 According to the "Physician's Desk Reference®", 53rd Edition, Copyright 1999 Medical Economics Company, Inc., page 2302, gabapentin is used for
15 adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin exists in a crystalline form and exhibits poor compressibility and compactibility. Compressibility is the ability of a powder to decrease in volume under pressure, while compactibility is the ability of a powder to be compressed into a tablet of a certain hardness or crushing
20 strength. These detrimental characteristics of gabapentin cause capping and lamination defects during compression of gabapentin into tablets. A capping defect means that there is partial or complete separation of the top or the bottom crowns of a tablet from the main body. A lamination defect means that there is a separation of a tablet in two or more layers.

25 The conventional approach to remedying these tableting problems is to introduce excipients as compression aids. However, the inclusion of additional excipients can adversely affect the stability of gabapentin. Also, the more excipients used in a composition the more expensive and time-consuming

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commercial production becomes. Furthermore, an increase in the amount of excipients results in an increase in the tablet size. Large tablets are uncomfortable to swallow and result in low patient compliance.

Excipients are substances used in combination with an active ingredient to produce a pharmaceutical formulation. Some examples of excipients are binders, lubricants, disintegrants, diluents, colorants, flavors, glidants, surfactants, absorbents and sweetening agents. Excipients often used as compression aids are binders. Binders are agents used to add cohesion to particles. Typically, materials used as binders are water-soluble derivatives of cellulose, gelatins, sugars, natural and synthetic gums, polyethylene glycol, pregelatinized starch, povidone, copolyvidone, waxes, and other suitable materials known to those skilled in the art.

The problem encountered with the inclusion of large amounts and/or number of excipients to a gabapentin formulation is that a number of excipients were not compatible with gabapentin and resulted in stability problems such as degradation. Gabapentin has been found to degrade into lactam, resulting in a decrease in the potency of gabapentin over time. Therefore, it is necessary to avoid degradation of gabapentin over the shelf life of the product. The shelf life of the product is generally two years from completion of manufacture. The level of degradation over the shelf life of the tablets can be determined by storing the product in closed containers for a three-month period at 45°C and 75% relative humidity. Tablets containing gabapentin should have no more than about 0.4% by weight of lactam as determined by High Performance Liquid Chromatography (HPLC) at the end this three-month period. Preferably, gabapentin tablets should contain no more than about 0.2% by weight of lactam. By using methods such as HPLC or Thin Layer Chromatography for the analysis of degradation products, including lactam, one may determine the compatibility of excipients.

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Another difficulty encountered in producing gabapentin tablets is that gabapentin is not amenable to traditional wet granulation techniques. Because the viscosity of the binder solution increases with an increase in the binder content, to apply a functional amount of binder for gabapentin, the amount of solvent has to be increased. This results in a wet granulation that is in a semi-liquid state and is not suitable for conventional drying methods. Therefore, the wet granulation technique has to be done in multiple stages where a portion of binder solution is added, followed by drying, then the next portion of binder solution and so forth. The wet granulation process is also conducted at elevated temperatures and accompanied by wetting gabapentin, which may be detrimental to the stability of gabapentin, cause polymorph conversion and change the crystalline structure of the active drug. This problem is eliminated by using a spray-coating method wherein a binder is dissolved in a solvent to form a binder solution which is then spray-coated on the drug particles. By using this method substantially all of the solvent is evaporated as it is applied, leaving a film of binder around the drug particles, and the process is conducted at or below room temperature.

In accordance with the present invention, spray-coating techniques are used to produce a compressible granulation containing gabapentin. Spray-coating gabapentin particles with a suitable binder solution produces a material that can be compressed into tablets having high hardness, low friability, and a size patients can swallow. Preferably, the pharmaceutical tablet comprises more than about 76% by weight of gabapentin. More preferably, the pharmaceutical tablet for commercial production comprises more than about 88% by weight of gabapentin. The tablets of the present invention can contain from about 500 mg to about 800 mg of gabapentin. More preferably the tablets will contain about 600 mg to 800 mg of gabapentin.

The spray-coating method of the present invention has application to other active drugs that exhibit poor compressibility and compactibility, are in tablet

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form, and require large doses for administration. Using a traditional wet granulation method to produce tablets containing large doses of active drug is inefficient and expensive because of the large amount of excipients and solvent needed to produce a suitable tablet. Furthermore, these excipients can affect the physical and chemical characteristics of the active drug rendering the product unsuitable for commercial production. By spray-coating the active drug particles with binder solution, the use of additional excipients can be avoided. Thus, tablets produced by this method exhibit acceptable physical and chemical characteristics while being small enough for a patient to swallow. A large dose of active drug is generally about 500 mg to about 1200 mg of drug content in a single tablet. The term active drug is defined as an active ingredient that is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans or other animals.

In the present invention any binder solution known to form a suitable spray solution can be used. For example, binders such as water-soluble derivatives of cellulose, gelatins, sugars, natural and synthetic gums, polyethylene glycol and combinations thereof, dissolved in a solvent such as ethanol, isopropyl alcohol, methanol, methylene chloride, acetone or combinations thereof, can be used. Preferably, the binder solution comprises hydroxypropyl cellulose dissolved in an alcohol, such as ethanol.

The solution may be prepared by any method that permits dissolution of binder to produce a homogenous solution, mixture or dispersion, such that formulations may be prepared that will contain a uniform amount of the binder. The concentration of binder in solution will depend upon the components used and the desired viscosity. For example, a binder solution can have up to 30% of povidone or copolyvidone. This binder solution is sprayed onto the gabapentin particles at a controlled temperature and airflow. Gabapentin is commercially available in a variety of particle size ranges such as about 10 μm to about 250 μm .

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Preferably the particle size range is about 25 μm to about 75 μm . Examples of suitable commercial spray-coating techniques are described, for example, in "Spray Drying Handbook", 4th ed., K. Masters, which is incorporated by reference.

5 A preferred method of spray-coating involves the use of fluid-bed processing equipment. Fluid-bed processing involves the use of air that passes up through the gabapentin particles and fluidizes them. The binder solution is applied to the particles through a pneumatically atomized nozzle equipped in the fluid-bed processing equipment. The solvent from the binder solution is concurrently
10 removed from the coated particles under controlled temperature and airflow conditions than can be obtained by routine experimentation. By maintaining the ratio of airflow to spray rate of binder solution, an isothermic process can be achieved. This allows the application of a large amount of binder solution in a one step process while eliminating excessive heat and moisture that can be
15 detrimental to the stability of gabapentin.

 The resulting spray-coated drug particles can be subjected to direct compression tabletting methods. Preferably, other excipients such as lubricants are blended into the particles by known methods to aid compression. Lubricants are agents that prevent adhesion of the tablet material to surfaces, including dies
20 and punches of the tablet press. Lubricants also reduce interparticle friction, facilitate ejection of the tablets from the die cavity and may improve the flow rate of the tablet material. Commonly used lubricants include, but are not limited to, talc, magnesium stearate, calcium stearate, stearic acid, waxes, hydrogenated vegetable oils and polyethylene glycol.

25 Optionally, disintegrants may also be added to the spray-coated drug particles. Disintegrants are agents that aid in the disintegration of the tablets and include, but are not limited to, starch, clays, microcrystalline cellulose, sodium starch glycolate, and cross-linked polymers, preferably, crospovidone. The

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amounts of each excipient used are conventional and can be determined by routine experimentation.

Compression into a tablet form can be accomplished by a tablet press. A tablet press includes a lower punch that fits into a die from the bottom and an upper punch having a corresponding shape and dimension which enters the die cavity from the top after the tableting material falls into the die cavity. The tablet is formed by pressure applied on the lower and upper punches. Typical compression pressures are about 6 kN to about 36 kN and will vary based on the desired size and hardness of the tablet. Preferably the compression pressure is about 8 kN to about 20 kN. Tablet presses and other compression devices are well known in the art.

For ease of swallowing, it may be desirable to coat the tablet containing gabapentin. Examples of acceptable commercial coating processes are described in "The Theory and Practice of Industrial Pharmacy, 3rd ed.", Lachman Lieberman, Kanig, pp. 359-373, which is incorporated by reference. Coating materials may include polymers such as hydroxypropyl methylcellulose, ethylcellulose, povidone, and polyethylene glycol; plasticizers such as castor oil, glycol and propylene glycol; and colorants such as dyes and lakes of dyes. Commercially available color coating systems such as Opadry® systems (Colorcon) may be also be used.

Capping and lamination are defects that appear during compression. A capping defect means that there is partial or complete separation of the top or bottom crowns of a tablet from the main body. A lamination defect means that there is separation of a tablet in two or more layers.

Friability and hardness are characteristics used to determine the mechanical strength of the tablets. Friability refers to the tablet resistance to surface abrasion. Hardness or crushing strength refers to the force required to fracture the tablet.

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The tablet must be of sufficient crushing strength or hardness to withstand the coating process without chipping or breaking. The hardness of the tablets prepared in accordance with the present invention can be measured by known methods as described, for example, in, "The Theory and Practice of Industrial Pharmacy, 3rd ed.", Lachman Lieberman, Kanig, incorporated herein by reference. Hardness or crushing strength is the amount of force required to fracture the tablet. Typically a larger tablet requires a higher hardness to withstand the mechanical shocks of processing as well as subsequent consumer handling. However, the hardness should not be so high that it adversely effects disintegration and dissolution rates of the tablets. Preferably, the hardness of the gabapentin tablets is about 10 kp to about 20 kp. More preferably, the hardness of the gabapentin tablets is about 14 kp to about 15 kp.

Another measure of durability of the tablet is the test for friability. Friability is the resistance to surface abrasions and is exemplified by tests which measure weight loss of the tablet by subjecting the tablets to standardized agitation procedures such as provided by the Roche Friabilator where the initial weight of tablets ($W(i)$) subjected to 100 free falls of 6 inches in a rotating drum are then weighed (W). The friability, f , is given by the formula, $f = 100 \times (1 - W/W(i))$. A friability values of about 1% is acceptable, but friability below about 0.8% is preferred.

The poor compactibility and compressibility properties of gabapentin are illustrated in FIG. 1 which is a plot of tablet hardness versus compression force for tablets made by: dry granulation (\blacktriangle), wet granulation (\bullet), and the present invention (\blacklozenge). The composition of the tablets is identical and differs only in the method of manufacture. The composition of the tablets comprise: 88.9% gabapentin, 3.5% hydroxypropyl cellulose, 5.8% crospovidone and, 1.8% calcium stearate (expressed as w/w of the tablet weight).

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In the dry granulation process, gabapentin, hydroxypropyl cellulose, crospovidone, and calcium stearate were sieved through a 20 mesh sieve and blended together in a V-blender. The resulting blend was then slugged on a tablet press using ½ inch round flat-faced punches. The slugs were ground through an
5 18 mesh sieve using an oscillator and then compressed into tablets. This process produced tablets that had low hardness and a friability of 100% because every tablet exhibited breakage such as capping. As FIG. 1 demonstrates, the tablets produced by this method had a maximum hardness less than 3 kp.

In the wet granulation process, gabapentin was placed in a high shear
10 mixer-granulator and mixed with a solution containing 10% hydroxypropyl cellulose in alcohol. The wet material was dried in a fluid-bed dryer and then milled through a comminuting mill equipped with a perforated plate with 0.0020" diameter holes. The milled material was placed back in the granulator and another portion of the hydroxypropyl cellulose solution was added while mixing. This wet
15 material was again dried and mixed. This cycle was repeated until all of the binder solution was incorporated into the granulation. The milled granules were then blended with crospovidone and calcium stearate in a V-blender and compressed into tablets on a high speed, force fed tablet press. Tablets produced by the wet granulation process achieved a maximum hardness of only 11 kp and
20 exhibited an unacceptable friability level of 2.0%. Furthermore, because of the multiple applications of binder solution and intermittent drying, the gabapentin particles were subjected to a large amount of moisture and heat which is detrimental to the stability of gabapentin.

Attempts to improve both the wet and dry granulation methods involved
25 the addition of compression aids such as microcrystalline cellulose, calcium phosphate salts or mannitol and increasing the ratio of binder to drug to 1:6. Although these attempts resulted in improved hardness, the tablets were too large and had a friability value approaching 100% due to abrasions and capping.

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The 600 mg tablets produced by the present invention achieved a desired hardness strength of 14 kp and a friability of 0.01 %. As shown in FIG. 2, the 600 mg tablets made in accordance with Example 1 had a range of 10 kp to 22 kp. The 800 mg tablets produced by the present invention achieved a desired hardness strength of 16 kp and a friability of 0.04 %. The hardness range of the 800 mg tablets made in accordance with Example 1 was 10 kp to 25 kp as show in FIG. 3. Furthermore, this one set spray-coat application of binder solution did not require excess excipients, moisture, or heat which can be detrimental to the stability of gabapentin.

The following Examples of this invention are for illustrative purposes and are not intended to limit the scope of the invention.

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TABLE 1

Composition of a 600 mg Gabapentin Tablet

| INGREDIENT | | AMOUNT PER TABLET |
|------------|---|-------------------|
| Gabapentin | | 600 mg |
| 5 | Hydroxypropyl Cellulose, NF 75-150 cps (Klucel LF) | 24 mg |
| | Crospovidone (Polyplasdone XL) | 39 mg |
| | Calcium Stearate | 12 mg |
| | TOTAL WEIGHT | 675 mg |

10

TABLE 2

Composition of a 800 mg Gabapentin Tablet

| INGREDIENT | | AMOUNT PER TABLET |
|------------|---|-------------------|
| Gabapentin | | 800 mg |
| 15 | Hydroxypropyl Cellulose, NF 75-150 cps (Klucel LF) | 32 mg |
| | Crospovidone (Polyplasdone XL) | 52 mg |
| | Calcium Stearate | 16 mg |
| | TOTAL WEIGHT | 900 mg |

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TABLE 3

Composition of a 800 mg Gabapentin Tablet

| INGREDIENT | AMOUNT PER TABLET |
|--------------------------------|-------------------|
| Gabapentin | 800 mg |
| 5 Copolyvidone | 32 mg |
| Crospovidone (Polyplasdone XL) | 52 mg |
| Calcium Stearate | 16 mg |
| TOTAL WEIGHT | 900 mg |

EXAMPLE 1

- 10 Gabapentin tablets of the present invention are produced by applying a coating of binder solution comprising hydroxypropyl cellulose dissolved in alcohol, through a pneumatically atomized nozzle. The binder solution containing 7.5% hydroxypropyl cellulose is prepared by slowly adding hydroxypropyl cellulose, to alcohol and mixing the solution at room temperature for
- 15 approximately 60 minutes or until the binder is uniformly dispersed and a clear homogenous solution is achieved.

Gabapentin, supplied by Teva Tech, Ltd (Israel) and having a particle size in the range of 10 μm to 125 μm , is loaded into the product container of a fluid-bed processor. The fluid bed parameters are set as follows:

- 20 Number of Nozzles: 1
- Inlet Air Temperature Set Point: 50° C
- Atomization Air Pressure: 2-4 Bar
- Process Air Volume Set Point Range: 100 cfm - 400 cfm
- Spray Rate Range: 100 g/min-300 g/min
- 25 Product Temperature: 12° C - 25° C

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The process air volume is set to 100 cfm and gabapentin is fluidized. When the product temperature reaches about 25° C to about 28° C, the binder solution is applied. This solution is introduced through a pneumatically atomized nozzle positioned in the expansion chamber of the fluid bed processor. The fluidized gabapentin particles are thus coated with the binder solution.

While spraying, the process air volume is increased until the product temperature is stabilized between 12° C – 25° C. Once all the binder solution is applied, the process air volume is set to 150 cfm and the temperature to about 35° C to dry the coated particles. Drying is complete when the loss on drying, determined by Computerized Moisture Analyzer Balance, is not more than 0.75%.

The spray-coated particles are then sized through a Comminuting Mill. These sized particles are mixed in a V-Blender with crospovidone and calcium stearate to produce a final blend. The final blend is then compressed into tablets on a force fed tablet press at a pressure of 12 kN to 14 kN. The hardness range of the 600 mg tablets was 13.3 kp to 14.9 kp with an average hardness of 14.2 kp. Optionally, the tablets can be aesthetically coated with an aqueous dispersion such as an Opadry® (Colorcon) color system.

As used in the claims, gabapentin shall mean gabapentin itself, gabapentin analogs, all pharmaceutically acceptable salts of gabapentin, all pharmaceutically acceptable salts of gabapentin analogs, all combinations of pharmaceutically acceptable salts of gabapentin, all combinations of pharmaceutically acceptable gabapentin analogs, or all combinations of gabapentin itself with its pharmaceutically acceptable salts.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. However, the invention which is intended to be protected is not to be construed as limited to the particular embodiments disclosed. Further, the embodiments described herein are to be regarded as illustrative rather than restrictive. Variations and changes

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may be made by others, and equivalents employed, without departing from the spirit of the present invention. Accordingly, it is expressly intended that all such variations, changes and equivalents which fall within the spirit and scope of the present invention as defined in the claims be embraced thereby.

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WHAT IS CLAIMED IS:

1. A pharmaceutical tablet comprising more than about 76% by weight of gabapentin.
2. A pharmaceutical tablet of claim 1 comprising more than about
5 88% by weight of gabapentin.
3. A pharmaceutical tablet of claim 1 where the tablet has a friability of less than 0.8%.
4. A pharmaceutical tablet of claim 1 where the tablet has a hardness of about 14 kp to about 16 kp.
- 10 5. A pharmaceutical tablet of claim 1 where the tablet has a lactam level of less than about 0.2%.
6. A pharmaceutical tablet comprising:
 - (a) more than about 76% by weight of gabapentin;
 - (b) a friability of less than about 1%;
 - 15 (c) a hardness of about 10 kp to about 20 kp; and
 - (d) a lactam level of less than about 0.4% by weight of the tablet.
7. A pharmaceutical tablet comprising more than about 76% by weight of gabapentin, the tablet being formed from particles of gabapentin spray-coated with a binder solution, mixed with a disintegrant, and a lubricant, and then
20 compressed into the tablet.

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8. A pharmaceutical tablet of claim 7 comprising more than about 88% by weight of gabapentin.

9. A pharmaceutical tablet of claim 7 where the binder solution is hydroxypropyl cellulose or copolyvidone dissolved in alcohol, the disintegrant is crospovidone and the lubricant is calcium stearate.

10. A pharmaceutical tablet comprising more than about 88% by weight of gabapentin, the tablet being formed from particles of gabapentin spray-coated with hydroxypropyl cellulose dissolved in alcohol, mixed with crospovidone, and calcium stearate, and compressed into the tablet.

10 11. A method of producing pharmaceutical tablet comprising:
(a) dissolving binder in a solvent to produce a binder solution;
(b) spray-coating the binder solution on gabapentin particles to achieve a spray-coated gabapentin; and
(c) compressing the spray-coated gabapentin into a tablet for oral
15 administration to a patient;

where the tablet contains more than about 76% by weight of gabapentin.

12. The method of claim 11 where the tablet contains more than about 88% by weight of gabapentin.

13. The method of claim 11 where the tablet has a friability of less than
20 1%

14. The method of claim 11 where the tablet has a hardness of about 10 kp to 20 kp.

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15. The method of claim 11 where the tablet has a lactam level of less than about 0.4% by weight of the tablet.

16. The method of claim 11 where the binder solution comprises hydroxypropyl cellulose or copolyvidone dissolved in alcohol.

5 17. The method of claim 11 further comprising adding a disintegrant and a lubricant to the spray-coated gabapentin.

18. The method of claim 17 where the disintegrant is crospovidone and the lubricant is calcium stearate.

10 19. A method of producing a pharmaceutical tablet comprising:
a) dissolving hydroxypropyl cellulose in alcohol to produce a binder solution;
b) spray-coating the binder solution on gabapentin particles to produce spray-coated gabapentin;
c) mixing the spray-coated gabapentin with crospovidone and calcium
15 stearate to obtain a final blend; and
d) compressing the final blend into a tablet for administration to a patient;
where the tablet contains more than about 88% by weight of gabapentin.

20 20. A method of producing a pharmaceutical tablet comprising:
(a) dissolving binder in a solvent to produce a binder solution;
(b) spray-coating the binder solution on active drug particles to achieve spray-coated active drug particles;

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- (c) compressing the spray-coated drug particles into a tablet for oral administration to a patient;

where the tablet contains about 500 mg to about 1200 mg of active drug.

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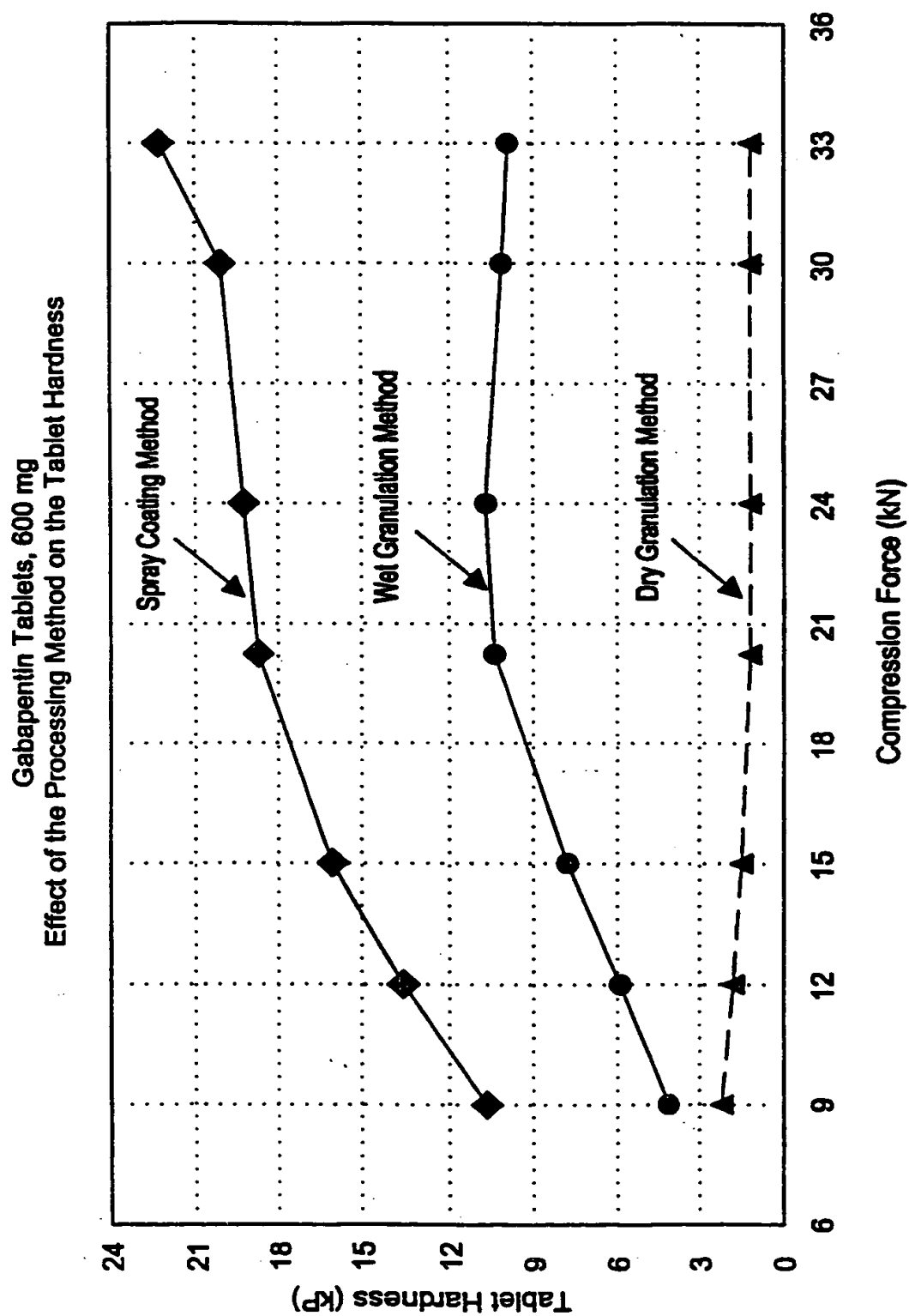


Fig. 1

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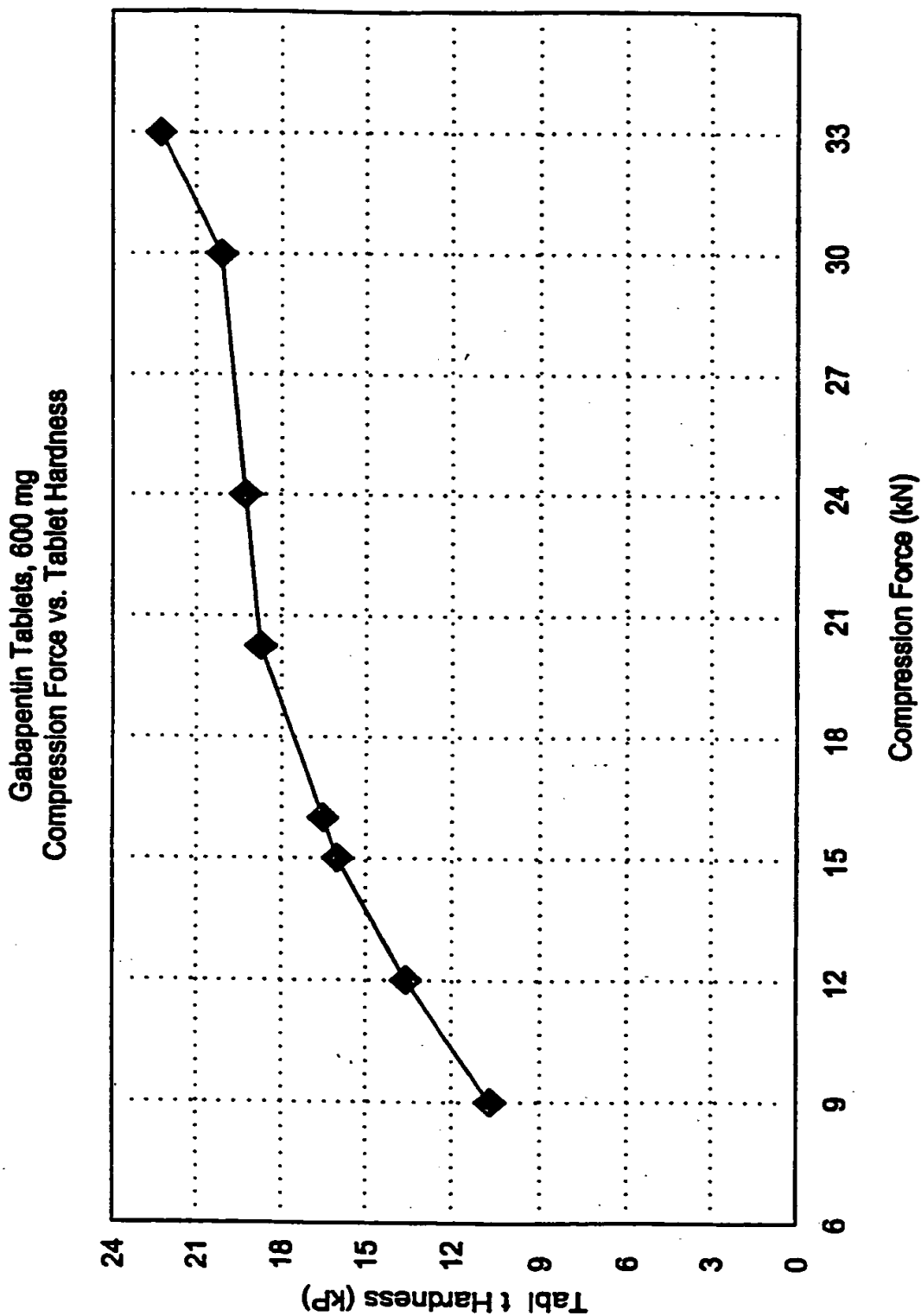


Fig. 2

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Gabapentin Tablets, 800 mg
Compression Force vs. Tablet Hardness

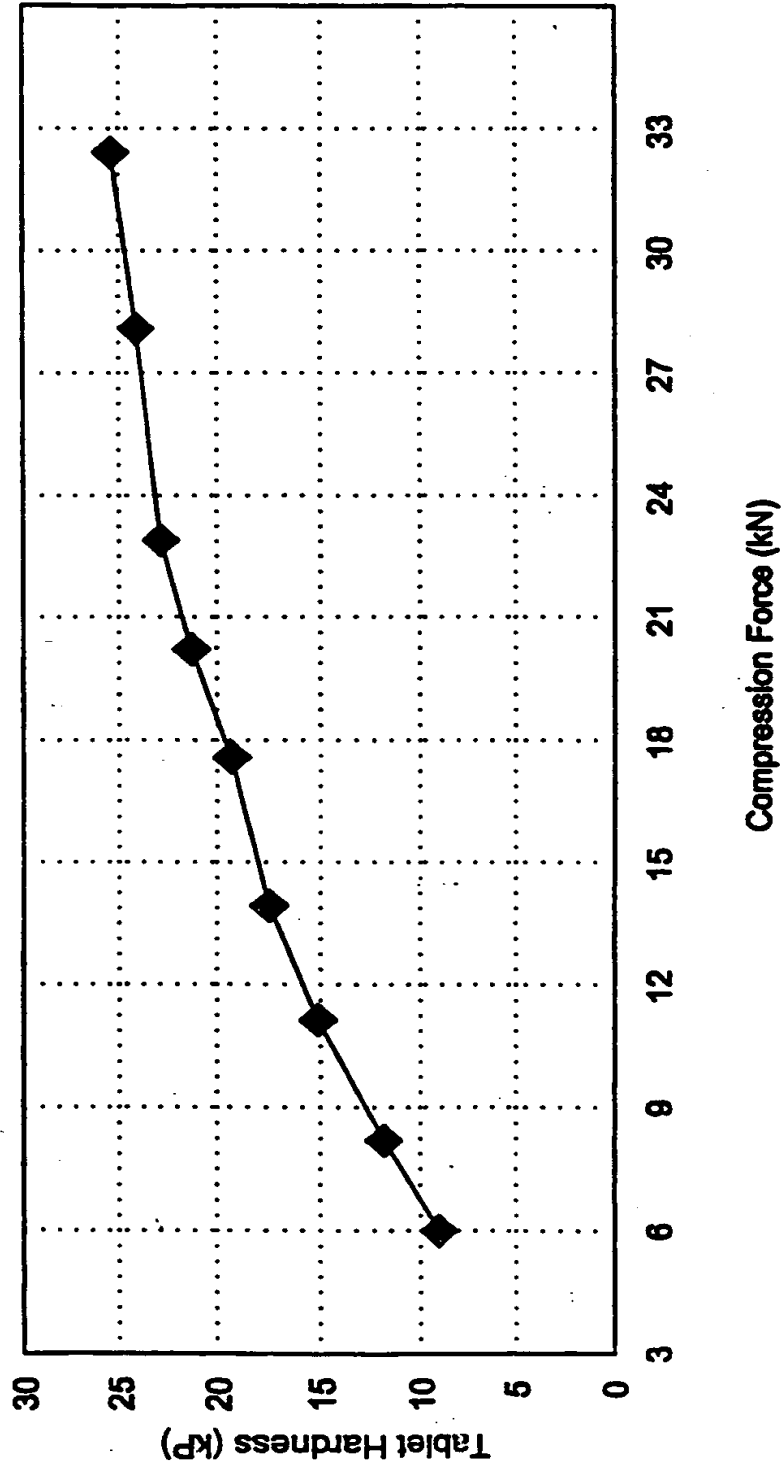


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/23017**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :A61K 9/20, 9/28, 9/32, 9/36, 9/42

US CL :424/464, 465, 474, 476, 480, 482

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464, 465, 474, 476, 480, 482

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST 2.0 search terms: gabapentin and tablet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | US 5,906,832 A (JAO et al) 25 May 1999, see column 5, lines 8-27, claim 1. | 1-6 |
| A | US 5,792,796 A (WOODRUFF et al) 11 August 1998, see example 3. | 1-20 |



Further documents are listed in the continuation of Box C.



See patent family annex.

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|--------------------------------------|--|--------------------------|--|
| * *A* *E* *L* *O* *P* | Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed | *T* *X* *Y* *A* | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family |
|--------------------------------------|--|--------------------------|--|

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|---|---|
| Date of the actual completion of the international search 20 SEPTEMBER 2000 | Date of mailing of the international search report 03 JAN 2001 |
| Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230 | Authorized officer JAMES M. SPEAR DELLA MAE COLLINS PARALEGAL SPECIALIST Telephone No. (703) 308-1233 TECHNOLOGY CENTER 1800 |